4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2021-N-0347]

Evaluating the Clinical Pharmacology of Peptides; Establishment of a Public Docket; Request for Information and Comments

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice; establishment of a public docket; request for information and comments.

SUMMARY: The Food and Drug Administration (FDA or Agency) is establishing a public docket to collect comments on evaluating the clinical pharmacology of peptides. For the purpose of this request, FDA is specifically interested in comments regarding the characterization of the effects of hepatic impairment, drug-drug interactions, and immunogenicity on the pharmacokinetics of peptides, as well as the effects of peptides on cardiac electrophysiology. However, there may be other clinical pharmacology considerations concerning the development of peptides. Public comments will help FDA develop recommendations for the design and conduct of studies important to the safe and effective use of peptides and facilitate the regulatory assessment of such studies.

DATES: Although you can comment at any time, to ensure that the Agency considers your comment in our development of recommendations, submit either electronic or written information and comments by **[INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*].**

ADDRESSES: You may submit comments and information at any time as follows:

Electronic Submissions

Submit electronic comments in the following way:

- Federal eRulemaking Portal: https://www.regulations.gov. Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to

https://www.regulations.gov will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on https://www.regulations.gov.

- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see "Written/Paper Submissions" and "Instructions").

Written/Paper Submissions

Submit written/paper submissions as follows:

- Mail/Hand delivery/Courier (for written/paper submissions): Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.
- For written/paper comments submitted to the Dockets Management Staff, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in "Instructions."

Instructions: All submissions received must include the Docket No. FDA-2021-N-0347 for "Evaluating the Clinical Pharmacology of Peptides; Request for Comments." Received comments will be placed in the docket and, except for those submitted as "Confidential Submissions," publicly viewable at https://www.regulations.gov or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday, 240-402-7500.

- Confidential Submissions--To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper

submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states "THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION." The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on https://www.regulations.gov. Submit both copies to the Dockets Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as "confidential." Any information marked as "confidential" will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA's posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: https://www.govinfo.gov/content/pkg/FR-2015-09-18/pdf/2015-23389.pdf.

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to https://www.regulations.gov and insert the docket number, found in brackets in the heading of this document, into the "Search" box and follow the prompts and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, 240-402-7500.

FOR FURTHER INFORMATION CONTACT: Jagan Parepally, Office of Clinical Pharmacology, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Silver Spring, MD 20993-0002, 301-796-1688.

SUPPLEMENTARY INFORMATION:

I. Background

FDA uses the term "peptide" to refer to polymers composed of 40 or fewer amino acids.[1] Peptides can be isolated from whole animal tissue, or produced in vitro, synthetically or through recombinant expression, and often serve as signaling molecules for many physiologic functions that are regulated by endogenous proteins. Peptides can exhibit distinct combinations of characteristics regarding their chemistry, pharmacology, sites of action, pharmacokinetic disposition, and pharmacodynamics. Although FDA has been regulating peptides for decades, there is a growing appreciation for specific considerations for the design and conduct of clinical pharmacology studies to assess peptides, such as those designed to evaluate the effects of organ impairment or drug interactions. Currently, there are no FDA-published guidance documents on clinical pharmacology assessments that contain specific recommendations for peptides.[2]

II. Request for Information and Comments

Interested persons are invited to provide detailed information and comments on certain aspects of evaluating the clinical pharmacology of peptides. For all questions, organize any discussion by the type of peptide (e.g., isolated from animal source, or produced in vitro, synthetically or through recombinant expression) and route of administration. Please provide the rationale for your suggestions and include supporting data if available. FDA is particularly interested in responses to the following overarching questions:

(1) Under what circumstances should the following assessments be warranted or not warranted for peptides?

(a) Evaluating pharmacokinetics-based drug-drug interactions (DDIs)

(b) Evaluating the pharmacokinetics in hepatic impairment

(c) Evaluating immunogenicity and its impact on pharmacokinetics, safety, and efficacy

(d) Evaluating QT prolongation

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[1] FDA Proposed Rule "Definition of the Term 'Biological Product'" (83 FR 63817 at 63821, December 12, 2018).
[2] There is an FDA draft guidance entitled "ANDAs for Certain Highly Purified Synthetic Peptide Drug Products That Refer to Listed Drugs of rDNA Origin" (October 2017) that is specific for ANDA applications for chemically synthetized peptides that refers to listed drugs of rDNA origin; available at https://www.fda.gov/media/107622/download.

(2) In circumstances where the assessments above are warranted, what types of assessments are suitable and why? What are the study design considerations (e.g., in vitro test systems, population, analytes, immunogenicity risk assessment, immunogenicity assay development and validation) for the types of assessments discussed in the following items? Please describe the rationale for any design considerations proposed.

(a) For evaluating pharmacokinetics-based DDIs (e.g., in vitro studies, dedicated clinical studies, including cocktail studies, population pharmacokinetic analyses), please discuss the advantages, challenges, and limitations for these assessments.

(b) For evaluating pharmacokinetics in hepatic impairment (e.g., dedicated clinical studies, population pharmacokinetic analyses), please discuss the advantages, challenges, and limitations for these assessments.

(c) For evaluating immunogenicity and its impact on pharmacokinetics, safety, and efficacy (e.g., antibodies against the active ingredient peptide, peptide-related impurities, or endogenous counterpart, if present, neutralizing activity and antibody titers, cytokine measurements), please discuss the advantages, challenges, and limitations for these assessments.

(d) For evaluating cardiac electrophysiology (e.g., hERG inhibition assay, thorough QT assessment) in nonclinical or clinical studies, please discuss the advantages, challenges, and limitations for these assessments.

(3) Are there other clinical pharmacology considerations for peptides not covered in the questions above, such as use of pharmacodynamic biomarkers and/or pharmacokinetic assessments for dose selection? If yes, provide a description and rationale for any proposed considerations, as well as approaches, advantages, challenges, and limitations for the assessment.

The public comments collected will help FDA develop recommendations for the design and conduct of clinical pharmacology studies important to the understanding of the safe and effective use of peptides and facilitate the regulatory assessment of such studies.

III. Electronic Access

Persons with access to the internet may obtain relevant clinical pharmacology guidances at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

Dated: May 7, 2021.

Lauren K. Roth,
Acting Principal Associate Commissioner for Policy.
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